A Meta-analysis of Depression During Pregnancy and the Risk of Preterm Birth, Low Birth Weight, and Intrauterine Growth Restriction

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Context: Maternal depressive symptoms during pregnancy have been reported in some, but not all, studies to be associated with an increased risk of preterm birth (PTB), low birth weight (LBW), and intrauterine growth restriction (IUGR).

Objective: To estimate the risk of PTB, LBW, and IUGR associated with antenatal depression.

Data Sources and Study Selection: We searched for English-language and non–English-language articles via the MEDLINE, PsycINFO, CINAHL, Social Work Abstracts, Social Services Abstracts, and Dissertation Abstracts International databases (January 1980 through December 2009). We aimed to include prospective studies reporting data on antenatal depression and at least 1 adverse birth outcome: PTB (<37 weeks’ gestation), LBW (<2500 g), or IUGR (<10th percentile for gestational age). Of 862 reviewed studies, 29 US-published and non–US-published studies met the selection criteria.

Data Extraction: Information was extracted on study characteristics, antenatal depression measurement, and other biopsychosocial risk factors and was reviewed twice to minimize error.

Data Synthesis: Pooled relative risks (RRs) for the effect of antenatal depression on each birth outcome were calculated using random-effects methods. In studies of PTB, LBW, and IUGR that used a categorical depression measure, pooled effect sizes were significantly larger (pooled RR [95% confidence interval] = 1.39 [1.19-1.61], 1.49 [1.25-1.77], and 1.45 [1.05-2.02], respectively) compared with studies that used a continuous depression measure (1.03 [1.00-1.06], 1.04 [0.99-1.09], and 1.02 [1.00-1.04], respectively). The estimates of risk for categorically defined antenatal depression and PTB and LBW remained significant when the trim-and-fill procedure was used to correct for publication bias. The risk of LBW associated with antenatal depression was significantly larger in developing countries (RR=2.05; 95% confidence interval, 1.43-2.93) compared with the United States (RR=1.10; 95% confidence interval, 1.01-1.21) or European social democracies (RR=1.16; 95% confidence interval, 0.92-1.47). Categorically defined antenatal depression tended to be associated with an increased risk of PTB among women of lower socioeconomic status in the United States.

Conclusions: Women with depression during pregnancy are at increased risk for PTB and LBW, although the magnitude of the effect varies as a function of depression measurement, country location, and US socioeconomic status. An important implication of these findings is that antenatal depression should be identified through universal screening and treated.

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revealed a relatively inconsistent and inconclusive picture.\textsuperscript{30} Some evidence indicates that depression during pregnancy may be significantly related to PTB,\textsuperscript{31,32} LBW,\textsuperscript{33,34} and IUGR,\textsuperscript{35} whereas other studies have reported no direct association.\textsuperscript{36-38} Reasons for these contradictory results are most likely related to differences in (1) study design methods, samples, sizes, and the timing, frequency, and type of antenatal depression measurement; (2) misclassification bias with respect to depression or birth outcomes; (3) the populations studied; and (4) the extent to which studies control for confounding factors of PTB, LBW, or IUGR such as socioeconomic status (SES), race/ethnicity, antidepressant use during pregnancy, smoking, substance abuse, previous preterm birth, or obstetric/medical complications.

We therefore conducted a meta-analysis of all available studies to quantify the strength of the relationships between depression during pregnancy and PTB, LBW, and IUGR and examined potential moderators of negative birth outcomes, such as categorical vs continuous measurement of antenatal depression, race or SES of the sample, and country location of the study (ie, whether the study was from the United States, a developing country, or a European social democracy). A social democracy was defined broadly as a democratic welfare state that incorporates both capitalist and socialist practices and provides universal access to health care.\textsuperscript{39,40} We expected that women with antenatal depression who lived in developing countries, relative to their peers in the United States or social democracies, would show greater disparities in the likelihood of PTB, LBW, and IUGR because of their more limited access to adequate prenatal, health, and mental health care.\textsuperscript{41} Similarly, we expected that socioeconomically disadvantaged, depressed, pregnant women within the United States would show a higher probability of negative birth outcomes compared with their middle- or upper-class counterparts because they have less access to ongoing adequate health and mental health services.\textsuperscript{42-44} Finally, given that categorical measures of antenatal depression more closely approximate clinical diagnoses of major depression than do continuous measures, we hypothesized that the former would show a stronger association with adverse birth outcomes.

**METHODS**

The methods for conducting and reporting the meta-analysis followed state-of-the-art guidelines.\textsuperscript{45-47}

**SEARCH STRATEGY AND STUDY SELECTION**

Study investigators (N.K.G., A.R.G., J.L.M., and W.J.K.) retrieved potential studies based on a literature search of English language and non–English-language articles from January 1980 through December 2009 using the MEDLINE, PsycINFO, CINAHL, Social Work Abstracts, Social Services Abstracts, and Dissertation Abstracts International databases. The time frame ensured that the applied standards for the categorical measures of depression were consistent with the *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition)\textsuperscript{48} or later criteria. We used the following keywords and their combinations: depression, depressive symptoms, pregnancy, prematurity, antenatal, prenatal, birthweight, birth weight, preterm birth, gestational age, fetal growth restriction, intrauterine growth restriction, and small-for-gestational age. Relevant articles were also identified through references of retrieved articles and contact with prominent investigators in the field.

Published and unpublished English-language and non–English-language observational studies were included in the meta-analysis if they assessed depressive symptoms or unipolar depression diagnoses by means of a depression-screening questionnaire or structured psychiatric interview at 1 or more times during pregnancy. Studies were included if they reported sufficient data to calculate an effect size between depressive symptoms/diagnoses and at least 1 adverse birth outcome: PTB, LBW, or IUGR. Studies were excluded if they used a retrospective design to measure antenatal depression, did not use a prospective or longitudinal design, combined unipolar and bipolar depression diagnoses to measure antenatal depression,\textsuperscript{39,40} or reported the same data on antenatal depression and PTB, LBW, or IUGR from a previous article. Of 862 reviewed studies, 29 published studies met the inclusion criteria.

**DATA EXTRACTION**

**Adverse Birth Outcomes**

Two investigators (one of whom was N.K.G.) reviewed all the studies. Standardized data collection forms were developed a priori for data extraction.\textsuperscript{41} In cases of disagreement in coding, we reached agreement through consensus. The mean percentage of disagreement in coding across all 29 studies included in the meta-analysis was 2.1% (95% confidence interval [CI], 1.6%-2.6%). When a report did not contain sufficient data to calculate an effect size, we contacted the primary author up to 3 times to obtain this information. Six of 9 authors contacted provided the requested data. The following types of studies\textsuperscript{31-38,50-70} (*Table 1*) were included in the meta-analysis: PTB (n=20), LBW (n=11), and IUGR (n=12). The latter included studies examining the keyword topics fetal growth restriction or small-for-gestational age. We extracted information from each study pertinent to each adverse outcome using the authors’ definition of clinical significance. Typically, PTB was defined as less than 37 weeks’ gestation, LBW was defined as less than 2500 g, and IUGR was defined as a fetal weight lower than the 10th percentile for gestational age as determined through an ultrasound.\textsuperscript{40,81} Alternatively, IUGR was defined in some studies as LBW controlling for gestational age,\textsuperscript{56,60,64} a fetal weight lower than the 15th percentile for gestational age,\textsuperscript{70} or a fetal weight lower than the 10th customized percentile.\textsuperscript{63}

**Study Characteristics and Antenatal Depression Measures**

Information extracted from each study included year of publication, mean maternal age, mean gestational age at first depression assessment, timing and frequency of antenatal depression measurement, country location, country rating of inequality of income distribution (ie, Gini coefficient\textsuperscript{61}), sample size, and the predominant (ie, >60% of the participants) race/ethnicity, SES, parity, marital status, educational level, and work status of the sample. We also recorded the type of antenatal depression measure used (ie, depression-screening questionnaire or structured psychiatric interview).

**Other Biopsychosocial Risk Factors for Adverse Birth Outcomes**

We coded the extent to which each study controlled for a group of variables observed in the literature to be risk factors for each
Table 1. Characteristics of Studies Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Source</th>
<th>Country/ Gender Coefficient</th>
<th>Sample Size</th>
<th>Sample SES</th>
<th>Race/ Ethnicity</th>
<th>Depression Measure</th>
<th>Assessment Times/ Trimesters</th>
<th>RR (95% CI)</th>
<th>Control Variables</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al. 2004</td>
<td>Sweden/25.0</td>
<td>1465</td>
<td>Mixed</td>
<td>White</td>
<td>PRIME-MD</td>
<td>Once/second</td>
<td>1.19</td>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>Berle et al. 2005</td>
<td>Norway/25.8</td>
<td>680</td>
<td>Mixed</td>
<td>White</td>
<td>HADS-D</td>
<td>Once/third</td>
<td>1.78</td>
<td>No</td>
<td>8</td>
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<tr>
<td>Chung et al. 2001</td>
<td>Hong Kong/43.4</td>
<td>642</td>
<td>Mixed</td>
<td>Chinese</td>
<td>BDI</td>
<td>Twice/first, second, and third</td>
<td>1.60</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>Cooper et al. 1996</td>
<td>United States/40.8</td>
<td>2593</td>
<td>Lower</td>
<td>Black</td>
<td>CES-D</td>
<td>Once/second and third</td>
<td>0.99-1.06</td>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>Deyan et al. 1999</td>
<td>France/32.7</td>
<td>392</td>
<td>Mixed</td>
<td>White</td>
<td>EPDS</td>
<td>Once/second</td>
<td>1.00</td>
<td>No</td>
<td>4</td>
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<tr>
<td>Deyan et al. 2006</td>
<td>United States/40.8</td>
<td>79</td>
<td>Mixed</td>
<td>White</td>
<td>EPDS</td>
<td>Once/second</td>
<td>4.90</td>
<td>Yes</td>
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<tr>
<td>Dole et al. 2003</td>
<td>Germany/28.3</td>
<td>896</td>
<td>Mixed</td>
<td>White</td>
<td>CES-D</td>
<td>Once/first and third</td>
<td>0.87-1.41</td>
<td>Yes</td>
<td>11</td>
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<tr>
<td>Evans et al. 2007</td>
<td>England/30.0</td>
<td>10967</td>
<td>Mixed</td>
<td>White</td>
<td>EPDS</td>
<td>Twice/first and third</td>
<td>1.29</td>
<td>Yes</td>
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<tr>
<td>Gavin et al. 2009</td>
<td>United States/40.8</td>
<td>3019</td>
<td>Mixed</td>
<td>White</td>
<td>CES-D</td>
<td>Once/second</td>
<td>1.26</td>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>Goldenberg et al. 1991</td>
<td>United States/40.8</td>
<td>1545</td>
<td>Lower</td>
<td>Black</td>
<td>CES-D</td>
<td>Once/second</td>
<td>2.00</td>
<td>Yes</td>
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<tr>
<td>Haas et al. 2005</td>
<td>United States/40.8</td>
<td>1619</td>
<td>Mixed</td>
<td>CES-D</td>
<td>Twice/first and third</td>
<td>0.94-2.46</td>
<td>Yes</td>
<td>11</td>
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<tr>
<td>Hedegaard et al. 1993</td>
<td>Denmark/24.7</td>
<td>5872</td>
<td>Mixed</td>
<td>White</td>
<td>GHQ</td>
<td>Twice/second and third</td>
<td>1.90-4.01</td>
<td>Yes</td>
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<tr>
<td>Hoffman and Hatch, 2003</td>
<td>United States/40.8</td>
<td>666</td>
<td>Mixed</td>
<td>White</td>
<td>CES-D</td>
<td>3/Second</td>
<td>1.07</td>
<td>Yes</td>
<td>10</td>
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<tr>
<td>Jesse et al. 2003</td>
<td>United States/40.8</td>
<td>119</td>
<td>Lower</td>
<td>White</td>
<td>2-item validated screening tool</td>
<td>3.19</td>
<td>Yes</td>
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<tr>
<td>Li et al. 2009</td>
<td>United States/40.8</td>
<td>791</td>
<td>Mixed</td>
<td>Mixed</td>
<td>CES-D</td>
<td>Once/first and second</td>
<td>1.60</td>
<td>Yes</td>
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<tr>
<td>Neggers et al. 2006</td>
<td>United States/40.8</td>
<td>3149</td>
<td>Lower</td>
<td>Black</td>
<td>CES-D</td>
<td>Once/second</td>
<td>1.30</td>
<td>Yes</td>
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<tr>
<td>Nordentoft et al. 1996</td>
<td>Denmark/24.7</td>
<td>2432</td>
<td>Mixed</td>
<td>White</td>
<td>GHQ</td>
<td>Once/second</td>
<td>1.90-1.10</td>
<td>Yes</td>
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<tr>
<td>Orr et al. 2002</td>
<td>United States/40.8</td>
<td>1399</td>
<td>Lower</td>
<td>Black</td>
<td>CES-D</td>
<td>Once/first and second</td>
<td>1.96</td>
<td>Yes</td>
<td>10</td>
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<tr>
<td>Paarlberg et al. 1999</td>
<td>The Netherlands/30.9</td>
<td>396</td>
<td>Mixed</td>
<td>White</td>
<td>HSCL</td>
<td>3/First, second, and third</td>
<td>1.03</td>
<td>Yes</td>
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<tr>
<td>Patel and Prince 2006</td>
<td>India/32.5</td>
<td>245</td>
<td>Lower</td>
<td>Indian</td>
<td>GHQ</td>
<td>Once/first and third</td>
<td>3.49</td>
<td>Yes</td>
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<tr>
<td>Perkin et al. 1993</td>
<td>United States/40.8</td>
<td>1515</td>
<td>Lower</td>
<td>White</td>
<td>GHQ</td>
<td>3/First, second, and third</td>
<td>1.48-2.83</td>
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<tr>
<td>Rahman et al. 2004</td>
<td>Pakistan/30.6</td>
<td>265</td>
<td>Lower</td>
<td>Pakistani</td>
<td>SCAN</td>
<td>Once/first and second</td>
<td>2.10</td>
<td>Yes</td>
<td>9</td>
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<tr>
<td>Rondon et al. 2003</td>
<td>Brazil/54.0</td>
<td>865</td>
<td>Lower</td>
<td>Brazilian</td>
<td>GHQ</td>
<td>3/Second</td>
<td>1.58</td>
<td>Yes</td>
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<tr>
<td>Steer et al. 1992</td>
<td>United States/40.8</td>
<td>389</td>
<td>Lower</td>
<td>Black</td>
<td>BDI</td>
<td>Once/first and third</td>
<td>1.07</td>
<td>Yes</td>
<td>5</td>
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<tr>
<td>Suri et al. 2007</td>
<td>United States/40.8</td>
<td>90</td>
<td>Mixed</td>
<td>...</td>
<td>SCID</td>
<td>2-Item validated screening tool</td>
<td>1.00</td>
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<tr>
<td>Wisner et al. 2009</td>
<td>United States/40.8</td>
<td>238</td>
<td>Mixed</td>
<td>SCID</td>
<td>Continuous/first, second, and third</td>
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<td>Zimmer-Gembeck and Helfand, 1996</td>
<td>United States/40.8</td>
<td>3073</td>
<td>Lower</td>
<td>Mixed</td>
<td>Nonvalidated</td>
<td>Once/first and second</td>
<td>1.65</td>
<td>Yes</td>
<td>8</td>
</tr>
</tbody>
</table>

Abbreviations: BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression scale; CI, confidence interval; ellipses, not available; EPDS, Edinburgh Depression Scale; GHQ, General Health Questionnaire; HADS-D, Hospital Anxiety and Depression Scale–Depression; HSCL, Hopkins Symptom Checklist; IUGR, intrauterine growth restriction; LBW, low birth weight; PRIME-MD, Primary Care Evaluation of Mental Disorders; PTB, preterm birth; RR, relative risk; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SCID, Structured Clinical Interview for DSM-IV; SES, socioeconomic status (as defined by income, educational level, or type of insurance).

Each row in this table describes an independent study of antenatal depression and adverse birth outcomes. Gini coefficient refers to the numerical coefficient indicating the degree of income inequality in each country (0=perfect equality; 100=perfect inequality). Effect sizes are represented by RRs and 95% CIs. Control variables include (1) demographic (age, SES, parity, race/ethnicity, educational level, marital status, work status, and sex of infant); (2) psychiatric (anxiety, stress, alcohol and substance abuse, selective serotonin reuptake inhibitor use, smoking, and previous depression or psychiatric illness); and (3) obstetric/medical (gestational age; prepregnancy body mass index; previous PTB, LBW, or IUGR; previous or current hypertension, diabetes, or preeclampsia; or other obstetric complications). Study quality ratings range from 0 to 12.

b $P < .05$.

c $P < .01$.

d Only the adult (≥18 years) sample was included in the meta-analysis.
adverse birth outcome, including demographic variables such as maternal age, SES, parity, race/ethnicity, educational level, marital status, work status, and sex of the infant; psychiatric variables such as antenatal anxiety, stress, drug/alcohol use, antidepressant medication use, and smoking; and obstetric/medical variables such as history of PTB or LBW, current gestational diabetes or preeclampsia, prepregnancy maternal weight or body mass index, and gestational age. We designated the following as key control variables because they have shown the strongest and most consistent associations with adverse birth outcomes in the literature: (1) smoking or substance abuse,10-11,85-89 (2) race/ethnicity or SES,62,90-98 (3) previous PTB87-90 and (4) selective serotonin reuptake inhibitor (SSRI) antidepressant use.90-94

Methodologic Quality Assessment

Two of the investigators (one of whom was N.K.G.) rated each study on 6 components of methodologic quality, which we developed by modifying the instrument by Downs and Black95 for randomized controlled trials and observational studies. We used a consensus approach in which any differences were resolved before assigning a final rating (intraclass correlation coefficient, 0.97; 95% CI, 0.93-0.98). The 6 components evaluated (1) the size of the sample, (2) the representativeness of the sample, (3) whether the sample was clearly described, (4) the internal validity of the measure used to assess antenatal depression, (5) whether the statistical tests were appropriate and controlled for the key variables described previously, and (6) whether the study response rate (ie, those who declined to enter the study) and attrition rate (ie, those who entered the study but dropped out) were reported and taken into account statistically. The 3 levels of quality for each component (not adequate, somewhat adequate, and adequate) received equal weights in scoring. A composite quality score was created for each study (Table 1), which was a sum of the number of the 6 components rated (total score range, 0-12).

DATA ANALYSIS

The association of antenatal depressive symptoms or diagnoses with each adverse birth outcome was examined using relative risks (RRs). To do this, we considered odds ratios (ORs) as surrogates for RRs because when outcomes undergoing study are relatively uncommon, the relative odds approximate RRs. One study57 used the correlation coefficient as the measure of effect size between antenatal depression and LBW; in this case, we computed the RR by means of transformation from the Pearson correlation to the standardized mean difference and then from this difference to the log OR.96 Two studies of PTB reported hazard ratios as a measure of association between antenatal depression and time to delivery. Because hazard ratios provide a control for calendar time, we consider an effect size derived from Cox regression as a measure of RR.97 For each birth outcome, there were a sufficient number of studies to calculate an effect size with a corresponding 95% CI.98 We weighted the study-specific RR by the inverse of its variance to compute a pooled RR using random-effects models. A 2-tailed P < .05 was used to determine statistical significance. Statistical analyses were performed with Comprehensive Meta-analysis version 2.2 (Biostat, Englewood, New Jersey) and SPSS version 17.0 (SPSS Inc, Chicago, Illinois) statistical software.

Heterogeneity of effect size was assessed using the Cochran Q statistic (P ≤ .10) and the I² statistic (a transformation of the Cochran Q that indicates the percentage of variation in the effect size estimate attributable to heterogeneity rather than sampling error).99 A nonsignificant I² statistic suggests that the obtained pooled RR represents a unitary effect and that any variability in effect sizes is caused by random error rather than the influence of other potential moderator variables. For outcomes in which the test of homogeneity of effect sizes was significant, random-effects meta-regression analyses and moderator analyses were conducted to determine whether 6 study characteristics could explain variability across studies: (1) country location: United States, developing country, or social democracy; (2) the country rating of inequality of income distribution (ie, Gini coefficient); (3) sample SES; (4) sample race (eg, black or white), controlling for SES; (5) study methodology; and (6) categorical vs continuous antenatal depression measurement. Sensitivity analyses100 (known as “leave-one-out”) were conducted by iteratively deleting each study and calculating the resulting effect sizes.

We followed a group of a priori decision rules for pooling data from each study. First, we used the most typical cutoff value for the validated depression scale in each study. Second, when the cutoff score was trichotomized, we used the typical cutoff value to determine the mean of the scores for the medium- and high-risk groups to comprise the group with depression. Third, when a study examined a depression-only group and a depression plus antidepressant medication group, we pooled the effect sizes for the 2 groups in the primary analysis. We then conducted sensitivity analyses100 for the studies that stratified for antidepressant medication use during pregnancy to compare the birth outcomes for depressed women treated and not treated with antidepressants. Fourth, for studies that measured depression more than once at different times or trimesters during pregnancy, we used the mean of the effect sizes in the primary analyses. Fifth, we used both categorical and continuous measures of antenatal depression in the primary analyses and then conducted moderator analyses based on the categorical-continuous distinction. Sixth, in the primary analyses we included 28 studies that used a validated measure of antenatal depression and an additional study that did not report validity or reliability data for its antenatal depression measure.10 We also conducted sensitivity analyses comparing the birth outcomes for the 28 studies using validated measures with the outcomes for the 29 studies used in the primary analyses.

Publication bias was assessed visually using a funnel plot and quantitatively using an adjusted rank correlation test101 and a regression procedure to measure funnel plot asymmetry.102 The trim-and-fill method by Duval and Tweedie103,104 was used to adjust for potential publication bias. The trim-and-fill method assesses asymmetry in the funnel plot, imputes the number of suspected missing studies, and recalculates the adjusted effect size estimate. The adjusted result can be used as a sensitivity analysis to indicate the extent to which publication bias may affect the pooled estimate.105

RESULTS

The study retrieval and selection strategy is illustrated in Figure 1. Of 862 citations meeting initial search criteria, 54 articles were retrieved and 3 were identified from the references of the retrieved articles, making a total of 57. Of these, 28 studies were excluded (23 studies met at least 1 of the exclusion criteria, and 5 studies represented duplicate studies in which the same data were reported in a previous article), leaving a total of 29 articles included in the meta-analysis. Table 1 gives the characteristics of the studies included in the meta-analysis.
ANTENATAL DEPRESSION AND RISK OF ADVERSE BIRTH OUTCOMES

Preterm Birth

Twenty studies evaluated the association between antenatal depression and PTB, with RRs ranging from 1.01 to 4.90 (Table 2). Eleven of the studies found no significant association. Using the random-effects model, depression during pregnancy was significantly associated with PTB (RR=1.13; 95% CI, 1.06-1.21). Significant heterogeneity across studies was noted ($Q_{19}=49.0; P<.001; I^2=61\%$).

Low Birth Weight

Eleven studies evaluated the association between antenatal depression and LBW with RRs ranging from 1.02 to 4.75 (Table 2). Six of the studies found no significant association. The random-effects meta-analysis showed that antenatal depression was significantly associated with LBW (RR=1.18; 95% CI, 1.07-1.30). Significant heterogeneity across studies was found ($Q_{10}=33.8; P<.001; I^2=70\%$).

Intrauterine Growth Restriction

Twelve studies evaluated the association between antenatal depression and IUGR, with RRs ranging from 0.69 to 11.28 (Table 2). Only 2 studies reported a significant association. The summary RR calculated from the random-effects model showed that antenatal depression was not significantly associated with IUGR (RR=1.03; 95% CI, 0.99-1.08). Significant heterogeneity across studies was noted ($Q_{11}=22.4; P=.02; I^2=51\%$).

MODERATORS OF OUTCOME

Moderator analyses were conducted to explore sources of heterogeneity (Table 3). As expected, studies of PTB, LBW, and IUGR that used a categorical depression predictor yielded larger ($P<.05$ for all) pooled RRs (1.39 [95% CI, 1.19-1.61], 1.49 [1.25-1.77], and 1.45 [1.05-2.02], respectively) than studies that used a continuous depression predictor (1.03 [1.00-1.06], 1.04 [0.99-1.09], and 1.02 [1.00-1.04], respectively). In PTB trials, heterogeneity among studies was reduced by the addition of the depression predictor moderator (categorical: $Q_{15}=24.6; P=.06; I^2=39\%$; continuous: $Q_{1}=4.7; P=.20; I^2=36\%$).

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Table 2. Effect of Antenatal Depression on Outcomes of PTB, LBW, and IUGR

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>Relative Risk (95% CI)</th>
<th>$P$ Value</th>
<th>Variance Explained, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB</td>
<td>20</td>
<td>1.13 (1.06-1.21)</td>
<td>&lt;.001</td>
<td>61</td>
</tr>
<tr>
<td>LBW</td>
<td>11</td>
<td>1.18 (1.07-1.30)</td>
<td>.001</td>
<td>70</td>
</tr>
<tr>
<td>IUGR</td>
<td>12</td>
<td>1.03 (0.99-1.08)</td>
<td>.14</td>
<td>51</td>
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</table>

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; LBW, low birth weight; PTB, preterm birth.

aPooled effect size was estimated using the random-effects model.
As expected, country location (developing nation, social democracy, or United States) was also a significant moderator of the association between antenatal depression and LBW (Table 3 and Figure 2). In developing nations, 2 studies of antenatal depression and LBW yielded a pooled RR of 2.05 (95% CI, 1.43-2.93). In studies from social democracies and the United States, the resulting summary RRs were 1.16 (95% CI, 0.92-1.47) and 1.10 (95% CI, 1.01-1.21), respectively. Significant heterogeneity was still present in US studies ($Q_{df}=18.7; P=.002; I^2=73\%$). A similar effect ($Q_{df}=7.1; P=.03$) was found after excluding 2 US studies that used a continuous depression predictor, which yielded a pooled RR of 1.50 (95% CI, 1.22-1.84), and that eliminated heterogeneity across US trials ($P=0.45; I^2=0\%$).

<table>
<thead>
<tr>
<th>Moderator</th>
<th>No. of Studies</th>
<th>Relative Risk (95% CI)$^a$</th>
<th>$P$ Value</th>
<th>Within Group</th>
<th>Between Group</th>
<th>Variance Explained, %</th>
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<td>PTB</td>
<td></td>
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<tr>
<td>Depression predictor</td>
<td>14</td>
<td>1.39 (1.19-1.61)</td>
<td>&lt;.001</td>
<td>24.6</td>
<td>.06</td>
<td>39</td>
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<tr>
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<td>24.6</td>
<td>.06</td>
<td>39</td>
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<tr>
<td>Continuous</td>
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<td>.05</td>
<td>4.7</td>
<td>.20</td>
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<td>Study location$^b$</td>
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<tr>
<td>European social democracy</td>
<td>5</td>
<td>1.37 (1.01-1.85)</td>
<td>.04</td>
<td>20.0</td>
<td>&lt;.001</td>
<td>80</td>
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<td>United States</td>
<td>14</td>
<td>1.10 (1.03-1.19)</td>
<td>.005</td>
<td>22.2</td>
<td>.05</td>
<td>41</td>
</tr>
<tr>
<td>Study quality$^c$</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>≤6</td>
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<td>10.0</td>
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<tr>
<td>&gt;6</td>
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<td>1.14 (1.06-1.24)</td>
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<td>37.4</td>
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<td>Effect size</td>
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<tr>
<td>Adjusted</td>
<td>16</td>
<td>1.18 (1.08-1.28)</td>
<td>&lt;.001</td>
<td>38.4</td>
<td>.001</td>
<td>61</td>
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<td>.18</td>
<td>7.0</td>
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<td>Study location$^d$</td>
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<td></td>
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<tr>
<td>Developing nation</td>
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<td>2.05 (1.43-2.83)</td>
<td>&lt;.001</td>
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<td>European social democracy</td>
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<tr>
<td>United States</td>
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<td>1.10 (1.01-1.21)</td>
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<td>18.7</td>
<td>.002</td>
<td>73</td>
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<td>Study quality$^c$</td>
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<tr>
<td>≤6</td>
<td>3</td>
<td>1.59 (0.63-4.00)</td>
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<tr>
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<tr>
<td>Adjusted</td>
<td>7</td>
<td>1.17 (1.06-1.30)</td>
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<td>29.0</td>
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<td>79</td>
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<tr>
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<td>IUGR</td>
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<tr>
<td>Depression predictor</td>
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<td>1.45 (1.05-2.02)</td>
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<td>.29</td>
<td>20</td>
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<tr>
<td>Developing nation</td>
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<td>2.22 (1.03-4.79)</td>
<td>.04</td>
<td>2.1</td>
<td>.14</td>
<td>53</td>
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<tr>
<td>European social democracy</td>
<td>3</td>
<td>1.02 (0.99-1.05)</td>
<td>.21</td>
<td>1.8</td>
<td>.41</td>
<td>0</td>
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<tr>
<td>United States</td>
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<td>1.03 (0.96-1.10)</td>
<td>.41</td>
<td>9.6</td>
<td>.09</td>
<td>48</td>
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<td>Study quality$^c$</td>
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<tr>
<td>≤6</td>
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<td>2.20 (0.26-18.80)</td>
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<td>2.6</td>
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<td>62</td>
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<tr>
<td>&gt;6</td>
<td>10</td>
<td>1.03 (0.98-1.08)</td>
<td>.30</td>
<td>17.3</td>
<td>.04</td>
<td>48</td>
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<tr>
<td>Effect size</td>
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<td></td>
<td></td>
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<tr>
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<td>19.4</td>
<td>.20</td>
<td>54</td>
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<tr>
<td>Unadjusted</td>
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<td>2.17 (0.24-19.60)</td>
<td>.49</td>
<td>2.7</td>
<td>.10</td>
<td>63</td>
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</tbody>
</table>

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; LBW, low birth weight; PTB, preterm birth.

a Pooled effect size was estimated using the random-effects model.
b Only 1 study was conducted in a developing nation.
c Study quality ratings range from 0 to 12.
d Pairwise effect of moderator for LBW: developing nation vs European social democracy, $Q_{df}=7.0; P=.01$; developing nation vs United States, $Q_{df}=10.7; P=.001$; European social democracy vs United States, $Q_{df}=0.2; P=.68$.
e Pairwise effect of moderator for IUGR: developing nation vs European social democracy, $Q_{df}=3.9; P=.048$; developing nation vs United States, $Q_{df}=3.8; P=.05$; European social democracy vs United States, $Q_{df}=0.0; P=.84$.

As expected, country location (developing nation, social democracy, or United States) was also a significant moderator of the association between antenatal depression and LBW (Table 3 and Figure 2). In developing nations, 2 studies of antenatal depression and LBW yielded a pooled RR of 2.05 (95% CI, 1.43-2.93). In studies from social democracies and the United States, the resulting summary RRs were 1.16 (95% CI, 0.92-1.47) and 1.10 (95% CI, 1.01-1.21), respectively. Significant heterogeneity was still present in US studies ($Q_{df}=18.7; P=.002; I^2=73\%$). A similar effect ($Q_{df}=7.1; P=.03$) was found after excluding 2 US studies that used a continuous depression predictor, which yielded a pooled RR of 1.50 (95% CI, 1.22-1.84), and that eliminated heterogeneity across US trials ($P=.45; I^2=0\%$).

Table 3 reveals a similar pattern for studies evaluating the association between antenatal depression and IUGR, with a significant pairwise difference in RR between developing nations and US studies.
developing countries and social democracies (P = .048) and a near significant pairwise difference in RR between developing countries and the United States (P = .05). These data indicate that depressed pregnant women in the developing world are twice as likely to experience IUGR as their European or US counterparts.

Limiting the analysis to the 10 US studies that used a categorically defined depression predictor showed a trend (Q = 3.54; P = .06) for antenatal depression to be associated with an increased risk of PTB among women of lower SES (RR = 1.69, 95% CI, 1.14-2.50) but not in women of middle- or upper-income status (RR = 1.13; 95% CI, 0.99-1.29).

Inequality of income across countries, study quality, type of depression severity measurement, and use of adjusted vs unadjusted effect size estimates were not significant moderators of PTB, LBW, or IUGR. Race was not a significant moderator of PTB in US studies of predominantly low SES populations. Type of IUGR measurement was not a significant moderator of outcome in IUGR studies. In the 5 studies of PTB for which stratification by antidepressant medication treatment during pregnancy was possible, the summary RR was comparable for depressed women treated and not treated with antidepressants.

**Leave-One-Out Analyses**

Sensitivity analyses revealed that no single study unduly influenced the pooled RR estimates of the association between antenatal depression and PTB, LBW, and IUGR (data available on request). In particular, leaving out the 1 study that did not report validity or reliability data for its measure of antenatal depression did not significantly alter the findings observed for LBW in the primary analyses.

**Publication Bias**

For all 3 outcome measures (PTB, LBW, and IUGR), visual inspection of funnel plots in which each study’s effect size was plotted against the standard error showed marked asymmetry, suggesting that small studies with negative results may not have been published. Formal testing using the regression intercept approach confirmed the possibility of publication bias for PTB (P < .001), LBW (P = .001), and IUGR (P = .008). As indicated in Table 4, the trim-and-fill adjusted RRs for each adverse birth outcome are generally lower than the unadjusted RRs. More important, however, the estimates of RR for categorically defined antenatal depression and PTB and LBW were robust to the effects of publication bias.

**Figure 2.** Effect of antenatal depression on the risk of low birth weight (LBW) in developing nations, European social democracies, and the United States. CI indicates confidence interval.

This meta-analysis showed that depression during pregnancy, regardless of the type of antenatal depression measurement (ie, categorical or continuous), is associated with modest but statistically significant risks of PTB and LBW. Furthermore, the estimates of risk for PTB and LBW from categorically defined antenatal depression appear resilient to the effects of publication bias. Sensitivity analyses showed that the magnitude of RR for these adverse birth outcomes was consistent within the set of 20 studies examining PTB and the set of 11 studies investigating LBW. Although the sizes of the significant RRs for PTB and LBW posed by antenatal depression are modest, the test of relevance in our study is not statistical significance but public health significance. That is, given the prevalence of antenatal depression in a population of pregnant women, what will be the likely burden of PTB or LBW for their infants? Thus, a relatively small effect size magnified by a large population base can have a considerable and noteworthy effect on public health.

We also found evidence that the type of depression measurement (categorical vs continuous) moderated the strength of the associations between antenatal depression and PTB, LBW, and IUGR, thereby eliminating or reducing the heterogeneity associated with these findings. Results for categorical measures of antenatal depression revealed that having major depression or clinically sig-
and in the United States experience a double-barreled threat: advantaged childbearing women in developing countries and women of lower SES. Thus, many socioeconomically disadvantaged pregnant women in the United States are also twice as likely to experience antenatal depression in context, we note that smoking was observed to have a dose-dependent relationship with PTB, with smoking more than 10 cigarettes a day shown to increase the likelihood of PTB between 33 and 36 weeks by 40% and of PTB at 32 weeks or less by 60%. Furthermore, in a cohort analysis of a large, ethnically diverse population, substance use disorders were associated with a 2.4-fold higher risk of PTB and a 3.7-fold higher risk of LBW, and black race increased the likelihood of PTB by 60% and of LBW by 2-fold. Thus, the magnitude of risk for PTB and LBW posed by antenatal depression is comparable to the risk of smoking 10 or more cigarettes a day for PTB but is relatively modest contrasted to the greater risks of black race and substance abuse associated with PTB and LBW.

Moderator analyses for country location revealed that the RR of delivering an infant with LBW or IUGR was higher among women from developing countries who experienced antenatal depression than their counterparts in the United States or social democracies. Moreover, in US studies, categorically defined antenatal depression tended to be associated with an elevated risk of PTB in women of predominantly lower SES but not in women of middle- or upper-income status. Pregnant women of lower SES in the United States are also twice as likely to experience antenatal major and minor depression as are women from middle- to upper-income strata. Whereas cross-cultural variability in the prevalence of perinatal depression certainly exists, estimates of the prevalence of perinatal depression in several developing countries are similar to the higher depression rates in pregnant US women of lower SES. Thus, many socioeconomically disadvantaged childbearing women in developing countries and in the United States experience a double-barreled threat: an increased risk of becoming depressed during their pregnancies and an increased likelihood of experiencing adverse birth outcomes once they have antenatal depression. Depressed pregnant women living near or below poverty levels are subject to large amounts of acute and chronic stress, such as living in unsafe neighborhoods, experiencing racial/ethnic or economic discrimination, and confronting food inadequacy in their households. At the same time, despite Medicaid or other public insurance coverage during pregnancy, their mental health problems are seldom accurately diagnosed and they often lack access to specialty mental health services.

Several potential direct and indirect causal pathways through which antenatal depression leads to adverse pregnancy outcomes have been proposed. One possibility is that prenatal stress or depression during pregnancy might promote adverse birth outcomes through the dysregulation of the hypothalamic-pituitary-adrenocortical axis, stimulating the release of stress hormones, such as cortisol and catecholamines. These biological changes may result in placental hypofusion and consequent restriction of oxygen and nutrients to the fetus, leading to fetal growth restriction and/or precipitation of PTB. Other mechanisms include the possibility that antenatal depression might compromise immune system functioning, which in turn may lead to a reproductive tract infection triggering PTB. The harmful public health effect of antenatal depression on birth outcomes is further heightened by evidence that depression during pregnancy is associated with risky but modifiable health practices, such as poor nutrition and hygiene, lack of motivation to obtain prenatal care or to follow medical recommendations, and smoking and/or alcohol and substance abuse, all of which adversely affect pregnancy outcomes.

Clearly, pregnancy is an important time to universally screen women for depression, especially those who are socioeconomically disadvantaged, and to improve their timely access to evidence-based prenatal and mental health services. Improved accuracy of diagnosis and treatment of antenatal depression combined with education about harmful but potentially modifiable lifestyle practices could lead to decreased rates of PTB and LBW.

### Table 4. Comparison of Unadjusted Pooled RRs and Trim-and-Fill Adjusted Pooled RRs

<table>
<thead>
<tr>
<th>Depression Predictor</th>
<th>No. of Studies</th>
<th>Unadjusted Pooled RR (95% CI)a</th>
<th>No. of Missing Studies</th>
<th>Trim-and-Fill Adjusted Pooled RR (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB Overall</td>
<td>20</td>
<td>1.13 (1.06-1.21)</td>
<td>10</td>
<td>1.07 (0.99-1.15)</td>
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<tr>
<td>Categorical</td>
<td>16</td>
<td>1.39 (1.19-1.61)</td>
<td>6</td>
<td>1.24 (1.04-1.47)</td>
</tr>
<tr>
<td>Continuous</td>
<td>4</td>
<td>1.03 (1.00-1.06)</td>
<td>1</td>
<td>1.03 (1.00-1.07)</td>
</tr>
<tr>
<td>LBW Overall</td>
<td>11</td>
<td>1.18 (1.07-1.30)</td>
<td>6</td>
<td>1.10 (1.00-1.22)</td>
</tr>
<tr>
<td>Categorical</td>
<td>9</td>
<td>1.49 (1.25-1.77)</td>
<td>4</td>
<td>1.34 (1.10-1.64)</td>
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<tr>
<td>IUGR Overall</td>
<td>12</td>
<td>1.03 (0.99-1.08)</td>
<td>4</td>
<td>1.03 (0.97-1.09)</td>
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<tr>
<td>Categorical</td>
<td>8</td>
<td>1.45 (1.05-2.02)</td>
<td>3</td>
<td>1.17 (0.82-1.68)</td>
</tr>
<tr>
<td>Continuous</td>
<td>4</td>
<td>1.02 (1.00-1.04)</td>
<td>2</td>
<td>1.00 (0.98-1.03)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IUGR, intrauterine growth restriction; LBW, low birth weight; PTB, preterm birth; RR, relative risk.

a Using random-effects models.
b Using random-random effects trim-and-fill models.
c Only 2 studies used a continuous depression predictor; the trim-and-fill algorithm requires 3 or more studies.
Reducing the rates of these adverse birth outcomes is a critically important public health issue. During childhood, PTB is associated with an increased risk of mortality; adverse medical outcomes including respiratory distress syndrome, cerebral palsy, chronic lung disease, vision and hearing loss, and neurodevelopmental disabilities; cognitive difficulties; and psychiatric problems, such as internalizing and externalizing behaviors and attention-deficit/hyperactivity disorder. Long-term consequences of PTB in adulthood include diminished rates of reproduction and, for women born preterm, an increased risk of next-generation PTB, fetal stillbirth, and infant mortality. Prench and adult outcomes related to LBW are also significant international representation. Our meta-analysis also included studies that varied in the extent to which they controlled for confounding factors related to PTB, LBW, and IUGR. For example, one-third of the studies (n = 10) controlled for SSRI use or reported that SSRI use was unlikely in their sample. An increasing number of women with depression are prescribed antidepressant medications during pregnancy. These medications, especially SSRIs, have been significantly linked with LBW in some but not all studies. Wisner et al recently found that infants who were continuously exposed to either SSRIs or major depression throughout the 3 trimesters of pregnancy were more likely to be born preterm than were infants with partial or no exposure. Differentiating between the effects of depression or depressive symptoms and the effects of antidepressants on birth outcomes is challenging because (1) researchers typically investigate the effects of one without controlling adequately for the other; (2) use of antidepressants during pregnancy occurs at different times, dosages, and durations; (3) recognition and treatment of depression by the physician is often associated with depression severity and persistence; and (4) depression is also associated with the use of additional prescription and nonprescription medications and other potential confounders, such as smoking or substance use disorders.

Finally, prior evidence has shown that key variables in addition to depression, such as substance use or abuse, race/ethnicity or SES, and previous PTB, are strongly and consistently predictive of negative birth outcomes. Most of the studies in our meta-analysis controlled for at least 2 of these key predictors, but few controlled for all of them. In addition, most of the studies did not control for stressful life events and other psychiatric comorbidities of depression, such as antenatal anxiety, which has been linked with adverse birth outcomes in some studies. A recent meta-analysis of anxiety symptoms and birth outcomes, however, did not show evidence of this association.

Only 5 of 29 studies in our meta-analysis assessed major depression during pregnancy by using diagnostic criteria adhering to or compatible with the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition). Most studies used relatively short screening tools to evaluate levels of depressive symptoms and set cutoff scores for describing clinically significant depressive symptoms. Although categorizing depressive symptom levels may be related to the diagnosis of clinically significant depression, it is not a substitute nor may it be as accurate as a structured interview. Finally, although we found possible publication bias, the findings of an elevated risk of PTB and LBW associated with categorically defined depression remained robust to trim-and-fill analyses that corrected for this bias.

Limitations of the studies reviewed suggest the need for a large prospective epidemiological study to simultaneously evaluate the RRs during pregnancy of depression, SSRI use, smoking, substance use disorders, key sociodemographic variables, obstetric/medical variables, and important behavioral health practices, including engagement in adequate prenatal and medical care and nutrition. Multiple assessments of major and minor antenatal depression should be performed, using criteria from the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) as well as measures assessing depression severity. The RRs of anxiety disorders and anxiety severity should also be assessed because these psychopathologic conditions typically accompany depression and were found to be related in some, but not all, studies to adverse birth outcomes. Ideally, this future study would prospectively gather data during the prepregnancy, pregnancy, and postpartum periods, considering that a broader perspective on a woman’s health status may be necessary to better understand the risk factors associated with harmful birth outcomes.

Our overall pattern of findings in this meta-analysis highlights the salient public health risk of PTB and LBW posed by antenatal depression, particularly for socioeconomically disadvantaged women in developing countries and in the United States. Furthermore, mounting evidence from this meta-analysis and other sources suggests that untreated major depression during pregnancy is as likely to lead to poor birth outcomes as is treatment with SSRIs. An important implication of these findings is that pregnant women should be universally screened for depression and provided guideline-level treatment before childbirth. Given that untreated antenatal depression is the most robust predictor of postpartum depression and has additional serious adverse consequences for infant and child development beyond harmful birth outcomes, women and their obstetrics professionals will need to weigh the costs and benefits of treating antenatal depression pharmacologically, especially when treatment with evidence-based psychotherapy is not available or desired.
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